

Performance Status, Prognostic Scoring and Parenteral Nutrition Requirements Predict Survival in Patients with Advanced Cancer Receiving Home Parenteral Nutrition

Niamh Keane;^{*,1} Konstantinos C. Fragkos;^{*,1} Pinal S. Patel;¹ Friderike Bertsch;¹ Shameer J. Mehta;¹ Simona Di Caro;¹ Farooq Rahman¹

¹Intestinal Failure Service, Gastrointestinal (GI) Services, University College London Hospitals NHS Foundation Trust, London UK

**These authors contributed equally to this manuscript*

Abstract

We describe a cohort of Home Parenteral Nutrition (HPN) patients with advanced cancer in order to identify factors affecting prognosis. Demographic, anthropometric, biochemical and medical factors, Karnofsky Performance Status (KPS), Glasgow Prognostic Score (GPS), and PN requirements were recorded. Univariate and multivariate analyses were performed including Kaplan-Meier curves, Cox Regression and correlation analyses. In total, 107 HPN patients (68 women, 39 men, mean age 57 years) with advanced cancer were identified. The main indications for HPN were bowel obstruction (74.3%) and high output ostomies (14.3%). Cancer cachexia was present in 87.1% of patients. The hazard ratio (HR) for upper gastrointestinal and ‘other’ cancers vs gynaecological malignancy was 1.75 (p=0.077) and 2.11 (p=0.05), respectively. KPS score, GPS, PN volume and PN potassium levels significantly predicted survival ($HR_{KPS \geq 50 \text{ vs } < 50} = 0.47$; $HR_{GPS=2 \text{ vs } GPS=0} = 3.19$). In multivariate analysis, KPS and GPS remained significant predictors (p<0.05), whilst PN volume reached borderline significance (p=0.094). Survival was not significantly affected by the presence of metastatic disease, previous or concurrent surgery, chemo-radiotherapy, or indication for HPN (p>0.05). Most patients passed away in their homes or hospice (77.9%). Performance status, prognostic scoring and PN requirements may predict survival in patients with advanced cancer receiving HPN.

Keywords: parenteral nutrition, advanced cancer, bowel obstruction, performance status, survival, clinical

Abbreviations

CI: confidence Interval

CRP: C-Reactive Protein

ESPEN: European Society for Clinical Nutrition and Metabolism

GPS: Glasgow Prognostic Score

HPN: home parenteral nutrition

HR: hazard ratio

IQR: Interquartile range

KPS: Karnofsky Performance Status

PN: parenteral nutrition

SD: standard deviation

UCLH: University College London Hospitals

WCC: White cell count

Introduction

Artificial nutrition may be indicated in malnourished oncology patients who cannot autonomously meet their nutritional requirements (1). In the last decade there has been an increased trend in referrals and this cohort currently represent the commonest indication for home parenteral nutrition (HPN) worldwide. Nevertheless, the use of long-term HPN in advanced/incurable (previously referred to as palliative) cancer patients remains controversial in the UK (1-6). Timely commencement of HPN is considered in advanced cancer patients with an acceptable quality of life who would die from malnutrition-related complications (and in some cases starvation) before tumour progression (3, 5, 7). Cachexia is prevalent in more than 50% of patients with advanced cancer and can lead to death in more than 10% of subjects (8-10).

Discrepancies in worldwide clinical practice relate to financial and ethical issues, differing clinician views, socio-cultural attitudes and religious beliefs. Appropriate and careful selection of patients to offer HPN is a crucial point for clinicians. It is generally accepted that HPN should not be considered in imminently dying patients. However, other cases are less clear and robust criteria and guidelines are lacking. Financially, it is difficult to estimate direct and indirect costs of HPN services considering the variation between countries. Nevertheless, many advocate that its use in this patients' cohort constitutes an unacceptable additional burden to already overstretched health economies (2, 4-6, 11). Finally, there is a paucity of high quality evidence about the true impact of HPN on survival, tumour progression, performance status and quality of life to guide clinical practice in advanced cancer, as randomised controlled trials would be unethical (2, 4-6, 11, 12).

Prevalence of HPN in patients with advanced cancers throughout the world reflects differing practices (2, 6, 13-15). For example, in Denmark and the UK the prevalence is less than 10% while Netherlands, Italy and the USA are greater than 50% (2, 5-7, 11, 16, 17). The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines (Grade C) suggest considering HPN in advanced cancer patients with intestinal failure if enteral nutrition is insufficient to meet nutritional requirements; expected survival due to tumour progression is over two to three months; it is expected that PN will stabilise or improve performance status and/or quality of life; and the patient desires PN (1, 7). The commonest indication for HPN in patients with advanced cancer is bowel obstruction, caused by intra- or extra-abdominal malignancy with intraperitoneal spread, which is usually subacute (1, 6). Although contentious, HPN may facilitate survival and augment the effectiveness of palliative chemo-radiotherapy. However, some authors contend that HPN is a burden to patients and possibly feeds the tumour (2, 6, 18).

Robust practical guidance is lacking in advanced cancer patients on HPN despite previous studies investigating prognostic factors (2, 3, 6, 13, 19-28). In the present study, we aim to examine the prognostic significance of performance status, type and site of tumour, previous or concurrent chemo-radiotherapy, anthropometric characteristics, nutritional and inflammatory status, demographic characteristics, serum biochemistry and prognostic indices based on a large cohort of patients with advanced cancer receiving HPN at University College London Hospitals (UCLH), UK.

Methods

Settings

UCLH is a 665-bed tertiary hospital in central London, UK, and a national referral centre for many types of cancer. HPN candidates were initially identified by primary teams (oncology, gynaecology, urology, gastroenterology, surgery) and referred to the multi-disciplinary Nutrition Support Team. In each case, the options and prognosis were carefully reviewed and discussed with the primary team and patient before initiating HPN. Follow-up was performed regularly (every 4-6 weeks) and as clinically relevant.

Population

All adult patients, 18 years or older, with advanced cancer discharged on HPN from UCLH from 1st of January 2006 to 15th of October 2016 were included in the analysis. Loss to follow-up was the single exclusion criterion. Data was collected retrospectively through UCLH electronic patients' records and the HPN databases held by the Nutrition Support team.

Data Collection

The following data were collected:

Demographics and Medical Factors: primary malignancy, presence of metastases (defined as disease at nonadjacent organs), surgery for malignancy, chemotherapy and/or radiotherapy before or during PN, main indication for HPN and the place of death.

HPN Requirements: duration of HPN, volume, nitrogen, glucose, lipid and lipid formulation, electrolytes and days per week of HPN. Patients received individualised formulae containing fluids, amino acids, glucose, lipids, minerals and trace elements.

Serum Biochemistry: C-Reactive Protein (CRP), white cell count (WCC), albumin, haemoglobin, sodium, potassium, magnesium, phosphate and adjusted calcium.

Performance Status: Karnofsky Performance Status (KPS) was assessed by the attending clinician and a score of 50 was used as cut-off for analyses, with over 50 indicating that the patient is unable to work but able to live at home and care for most personal needs with varying amount of assistance needed (29, 30).

Prognostic Scoring: Glasgow Prognostic Score (GPS) was calculated and is based on the serum levels of albumin and CRP. A score of 2 is allocated when both an elevated CRP level (>10 mg/L) and hypoalbuminemia (<35 g/L) are present (31).

Anthropometric Characteristics: Habitual body weight, height, habitual BMI, weight upon starting PN, percentage of weight loss when PN commenced (from usual weight), BMI when PN commenced, weight at follow-up outpatient appointments at 3 and 6 months after discharge. Patients were defined as having cancer cachexia if weight loss $> 5\%$ (in absence of simple starvation) was reported or BMI < 20 kg/m² and any degree of weight loss $> 2\%$ (32).

Timeline: The day that HPN started (i.e. discharge date or baseline date) was considered as the starting time point for all measurements including anthropometrics, blood tests, and HPN requirements. End time point was date of death or censoring date (15 October 2016). Survival was reported in weeks.

Ethical Considerations

Individual patient data were anonymized and regulatory approval was granted by the site institutional review board. This study involved the collection of existing data and records. Informed consent was exempted according to the decision of institutional ethics board committees. This is a retrospective study and adherence to the principles of the Declaration of Helsinki was followed during design and analysis.

Statistical Analysis

Data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous data and absolute and relative frequency for categorical data, respectively. Overall survival was calculated from the onset of HPN until death irrespective of cause or censoring date on 15 October 2016. Univariate analyses were conducted with chi-square test, Spearman's rho for correlations, t-tests and ANOVA. After Kaplan-Meier analysis on the impact of the variables on survival, the groups were compared with the log-rank test. Variables that showed a p -value of ≤ 0.05 in the univariate analysis were included into Cox regression analyses. A p -value ≤ 0.05 was considered significant. For data analysis, IBM SPSS Statistics (Release 22.0.0. 2010, Chicago (IL), USA: SPSS, Inc., an IBM Company) was used.

Results

Patient Characteristics

Demographics and Medical Factors. Our sample included 107 patients (68 females, 39 males) with mean age 57 ± 12 years. Malignancy types and frequencies are shown in Table 2. Most patients had metastatic disease (81.3%) and had undergone surgery for their malignancy (79 %), or chemotherapy before and/or during PN administration (90.4 %). The majority of patients were radiotherapy naive (71.2 %). Most patients passed away in their homes or hospice (77.9 %) (Table 1).

HPN characteristics. The majority of patients had solely HPN (97.1 %), while 3 % required additional intravenous fluids. Median duration of HPN was 12.9 weeks (5.6-29.0). The main indications for HPN were bowel obstruction (74.3 %) and high output ostomies (14.3 %). The majority of patients were PN-dependent until death (Table 1). Average HPN requirements are shown in Table 3.

Anthropometrics. Mean BMI was 19.9 ± 4.1 kg/m² with 41.8% of patients being underweight BMI ≤ 18.5 kg/m²). Documented weight loss was greater than 10 % and 30 % in 58.1 % and 11.3 % of patients, respectively. Cancer cachexia was present in 87.1 %. Mean weight on discharge was 55.3 ± 12.3 kg with a relative increase up to 58.6 ± 11.3 kg at 6 months in the outpatient setting (Table 1).

Performance status and prognostic score. Mean KPS score was 50 ± 16 ; 66 % of patients scored KPS 50 to 80. GPS was 2 for most patients (34.6 %) (Table 1).

Serum Biochemistry. On discharge, mean CRP was high at 46 ± 48.3 mg/L (normal range 0-5.0) with normal WCC ($9.6 \pm 6.8 \times 10^9$ /L, normal range 3.0-10.0) and albumin borderline low at 32.2 ± 6 g/L (normal range 34-50). Mean haemoglobin was slightly below normal (101.6 ± 15 g/L, normal range 115-155) and mean values of electrolytes were within normal values (Table 1).

Table 1. Patient Characteristics.

Variables	Results
General Characteristics	
<i>Age (years)*</i>	
≤ 35	3 (2.8)
36 – 49	24 (22.4)
50 – 64	48 (44.9)
65 – 79	30 (28)
≥ 80	2 (1.9)
<i>Gender*</i>	
Female	68 (63.6)
Male	39 (36.4)
<i>Type of malignancy*,†</i>	
Gynaecological	37 (34.6)
Upper Gastrointestinal	21 (19.6)
Lower Gastrointestinal	24 (22.4)
Hepato-pancreatobiliary	10 (9.3)
Haematological	5 (4.7)
Other	10 (9.3)
<i>GPS*</i>	
0	10 (9.3)
1	19 (17.8)

Variables	Results
2	37 (34.6)
Not available (n/a)	41 (38.3)
HPN Characteristics	
<i>HPN Indication*</i>	
Bowel Obstruction	78 (74.3)
High Output Ostomy	15 (14.3)
Other [‡]	12 (11.4)
<i>HPN days per week*</i>	
4	5 (4.7)
5	2 (1.9)
7	100 (93.4)
<i>PN lipid type*</i>	
SMOF	34 (38.2)
Other [§]	55 (61.8)
<i>HPN termination reason*</i>	
Death	93 (94.9)
Established on oral / enteral feeding	4 (4.1)
Patient declined	1 (1)
Anthropometrics	
<i>Usual weight (kg)[¶]</i>	65.3 ± 14.6 (n = 65)
<i>Height (m)[¶]</i>	1.7 ± 0.1 (n = 71)
<i>Usual BMI (kg/m²)[¶]</i>	23.5 ± 4.8 (n = 63)
<i>Weight upon starting PN (kg)[¶]</i>	55.3 ± 12.3 (n = 71)
<i>% weight loss upon starting PN[¶]</i>	15.2 ± 11.5 (n = 62)
<i>% weight loss upon starting HPN*</i>	
< 20%	42 (67.7)
20% – 30%	13 (21)
> 30%	7 (11.3)
<i>BMI upon starting PN (kg/m²)[¶]</i>	19.9 ± 4.1 (n = 67)
<i>Weight in outpatient clinic, 0-3 months (kg)[¶]</i>	54.5 ± 9 (n = 37)
<i>Weight in outpatient clinic, 3-6 months (kg)[¶]</i>	58.6 ± 11.3 (n = 19)
Serum Biochemistry	
<i>Sodium (mmol/L, 135-145)[¶]</i>	136 ± 4 (n = 66)
<i>Potassium (mmol/L, 3.5-5.1)[¶]</i>	4.4 ± 0.5 (n = 66)
<i>Magnesium (mmol/L, 0.60-1.00)[¶]</i>	0.80 ± 0.10 (n = 63)
<i>Phosphate (mmol/L, 0.87-1.45)[¶]</i>	1.20 ± 0.20 (n = 65)
<i>Adjusted calcium (mmol/L, 2.20-2.60)[¶]</i>	2.40 ± 0.10 (n = 66)

* N (%)

[†] Gynaecological: breast, ovarian, endometrial, cervical; Lower gastrointestinal: small bowel, appendix, colon, sigmoid, rectal, anal; upper gastrointestinal: oesophageal, gastric, duodenal; hepato-pancreatobiliary: liver, pancreas, bile ducts; haematological: leukaemia, lymphoma; others: peritoneal, bladder, sarcoma, thyroid.

[‡] This included mucositis, graft-versus-host disease, radiation-related bowel disease, intra-abdominal collection, enterocutaneous fistula, malabsorption, intolerance or inability of enteral feeding.

[§] This included Clinoleic, Intralipid, Lipofundin and Triomel.

[¶] Mean ± SD

Survival: Univariate Analyses and Cox Regression

Overall mean survival was 30.8 weeks (95% CI 21.4-39.6) and median survival was 14 weeks (IQR 5-34). At the time of analysis, 88.8% had passed away, 3-month survival was 49.5% and 6-month survival was 30.8%. Univariate analyses are shown in Table 4. Kaplan-Meier curves for type of malignancy, HPN indication, KPS score, GPS, PN volume, and PN potassium content are shown in Figure 1 and for the rest of the variables in the Supplementary Materials (Supplementary Figures 1 and 2). Post-hoc power analyses were performed for the current sample size and significance level 0.05, revealing power over 80% for most predictors in the present sample.

Demographics: Age and gender did not significantly predict survival ($p > 0.05$) (Table 2).

Medical factors: The incidence of death in patients with upper gastrointestinal (HR = 1.75, $p = 0.077$) and ‘other’ malignancies (HR = 2.11, $p = 0.05$) was significantly higher compared to patients with gynaecological malignancy. Metastatic disease, surgery, chemo-radiotherapy, or indication for HPN did not significantly affect survival ($p > 0.05$).

Performance status and prognostic scoring: KPS score and GPS significantly predicted survival. A higher KPS score was associated with longer survival (median survival was 20 weeks vs 5 weeks, for KPS ≥ 50 vs KPS < 50 respectively; HR = 0.47, $p = 0.001$). A GPS of 0 was associated with longer survival than a GPS of 2 (median survival: 55 weeks vs 10 weeks, respectively; HR = 3.19, $p = 0.006$).

Anthropometrics: Weight, height, and BMI did not significantly correlate with survival.

Serum Biochemistry: The only significant predictors of survival were CRP (HR = 1.01, $p = 0.001$) and WCC (HR = 1.06, $p = 0.011$). There was a trend suggesting improved survival in patients with a serum sodium above 135 mmol/L (HR = 0.62, $p = 0.097$) and higher albumin levels (HR = 0.96, $p = 0.052$).

HPN requirements. Daily PN volume and potassium content predicted overall survival. An HPN volume of 2 L/day or more was associated with a significantly increased incidence of death (86%) compared to less than 2 L/day (median survival: 12 vs 34 weeks, respectively). An HPN potassium of 60 mmol/day or more was associated with a significantly increased incidence of death (81%) compared to a potassium content less than 60 mmol/day (median survival 10 vs 24 weeks, respectively). The type of HPN lipid (SMOFLipid (33) vs other) did not predict survival.

All statistically significant predictors associated with survival at univariate analysis were entered into a multivariate Cox regression model (Table 2). After adjusting for confounders (PN volume and PN potassium content), only KPS and GPS remained significant predictors of survival, whilst HPN volume reached borderline significance ($p = 0.087$). Higher scores of KPS and lower GPS were both associated with better survivals.

Spearman’s rho correlations of survival with CRP (rho = -0.484) and GPS (rho = -0.444) indicated a moderate association, while WCC (rho = -0.300), albumin (rho = 0.338), KPS (rho = 0.374), and PN potassium content (rho = -0.247) were weakly correlated with survival. All correlations were significant ($p < 0.05$) (Supplementary Table 1).

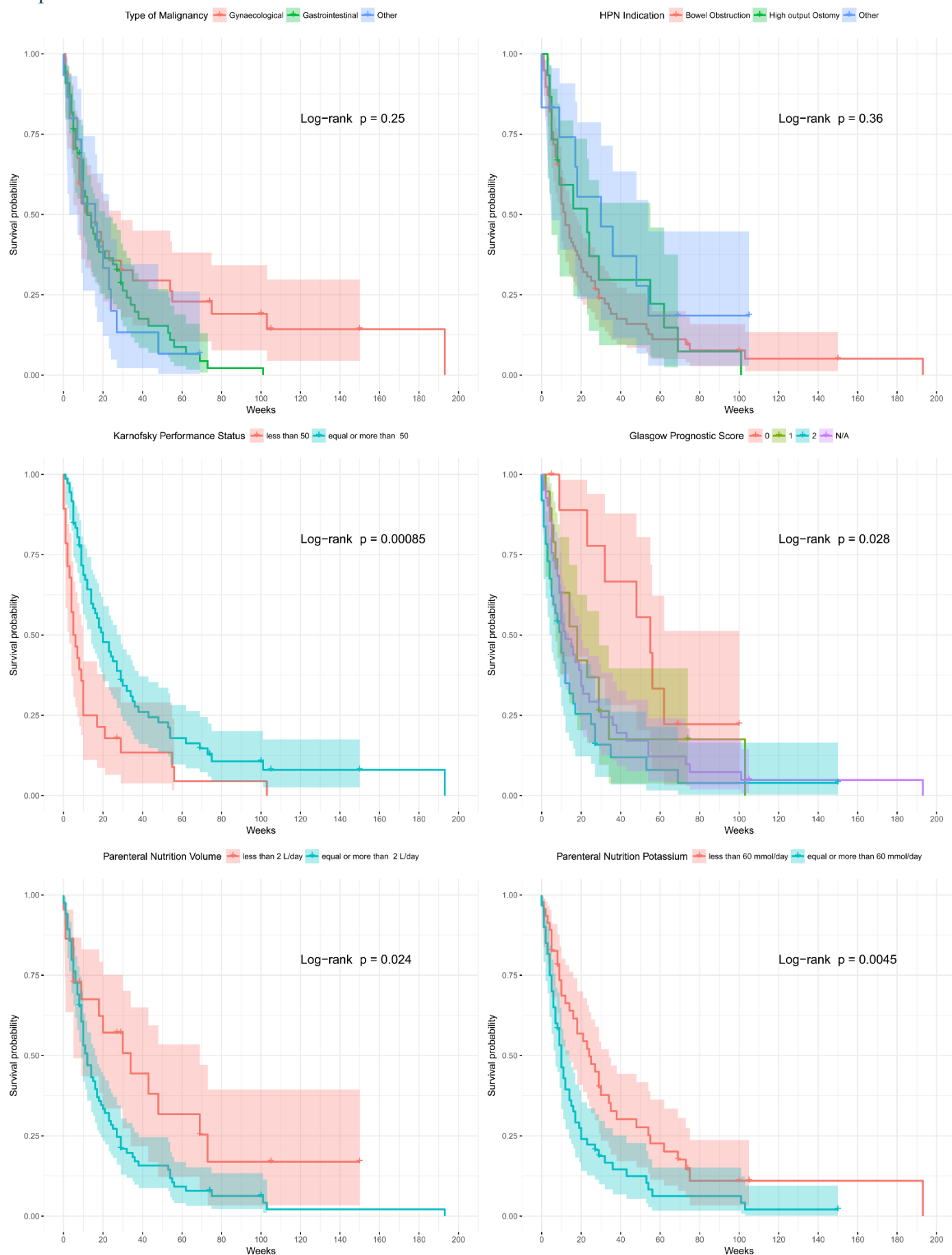
Table 2. Survival times and Cox regressions.

Variables	Survival (weeks)	Univariate Cox regression		Multivariate Cox regression	
	Median (IQR)	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Demographic characteristics					
<i>Age (years)</i>					
< 50	16 (9-36)	Ref.		--	--
50-64	10 (5-29)	1.08 (0.66-1.77)	0.755	--	--
≥ 65	14 (5-29)	1.02 (0.59-1.77)	0.938	--	--
<i>Gender</i>					

Variables	Survival (weeks)	Univariate Cox regression		Multivariate Cox regression	
	Median (IQR)	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Female	16 (5-34)	Ref.		--	--
Male	11 (5-32)	1.22 (0.80-1.86)	0.358	--	--
Medical Factors					
<i>Type of malignancy</i>					
Gynaecological	14 (5-55)	Ref.		--	--
Upper Gastrointestinal	10 (4-34)	1.75 (0.94-3.26)	0.077	--	--
Lower Gastrointestinal	12 (9-29)	1.38 (0.80-2.40)	0.251	--	--
Hepatobiliary	18 (10-43)	1.21 (0.59-2.52)	0.603	--	--
Haematological	17 (9-48)	0.95 (0.33-2.71)	0.916	--	--
Other	10 (3-23)	2.11 (1.00-4.45)	0.050	--	--
<i>Metastatic disease</i>					
No	18 (9-48)	Ref.		--	--
Yes	12 (5-32)	1.38 (0.79-2.39)	0.259	--	--
<i>Surgery</i>					
No	16 (7-23)	Ref.		--	--
Yes	14 (5-36)	0.84 (0.50-1.41)	0.500	--	--
<i>Chemotherapy</i>					
No	23 (16-29)	Ref.		--	--
Yes	12 (6-35)	0.92 (0.47-1.79)	0.797	--	--
<i>Radiotherapy</i>					
No	14 (6-29)	Ref.		--	--
Yes	15 (5-69)	0.65 (0.40-1.060)	0.086	--	--
<i>HPN indication</i>					
Bowel obstruction	12 (6-29)	Ref.		--	--
High output ostomy	23 (5-55)	0.88 (0.49-1.56)	0.659	--	--
Other	30 (9-54)	0.61 (0.31-1.230)	0.170	--	--
Anthropometrics					
<i>Usual weight (kg)</i>		1.002 (0.98-1.02)	0.815	--	--
<i>Height (m)</i>		12.6 (0.53-297.49)	0.117	--	--
<i>Usual BMI (kg/m²)</i>		0.97 (0.92-1.04)	0.420	--	--
<i>Weight upon starting PN (kg)</i>		1.01 (0.99-1.04)	0.192	--	--
<i>% weight loss upon starting HPN</i>					
< 20%	14 (4-35)	Ref.		--	--
between 20% and 30%	9 (7-25)	1.02 (0.52-1.99)	0.956	--	--
≥ 30%	30 (9-103)	0.64 (0.26-1.55)	0.325	--	--
<i>BMI (kg/m²) upon starting HPN</i>					
BMI ≤ 18.5	15 (7-32)	Ref.		--	--
BMI > 18.5	16 (4-35)	1.03 (0.61-1.74)	0.921	--	--
<i>Cancer cachexia</i>					
No	14 (8-29)	Ref.		--	--
Yes	14 (6-35)	1.09 (0.49-2.43)	0.827	--	--
<i>Weight (kg) in outpatient clinic, 0-3 months</i>		1.02 (0.97-1.06)	0.496	--	--
<i>Weight (kg) in outpatient clinic, 3-6 months</i>		1.02 (0.97-1.06)	0.506	--	--
Performance status					
<i>KPS Score</i>					
< 50	5 (2-10)	Ref.		Ref.	
≥ 50	20 (9-43)	0.47 (0.30-0.75)	0.001	0.49 (0.30-0.80)	0.004
Prognostic Scores					
<i>GPS</i>					

Variables	Survival (weeks)	Univariate Cox regression		Multivariate Cox regression	
	Median (IQR)	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
0	55 (32-62)	Ref.		Ref.	
1	18 (7-34)	2.00 (0.82-4.91)	0.129	1.91 (0.77-4.75)	0.162
2	10 (3-25)	3.19 (1.39-7.32)	0.006	3.60 (1.52-8.55)	0.004
N/A	12 (6-30)	2.26 (1.01-5.08)	0.049	2.46 (1.06-5.71)	0.036
Serum Biochemistry					
<i>CRP (mg/L)</i>		1.01 (1.004-1.015)	0.001	--	--
<i>WCC (x 10⁹/L)</i>		1.06 (1.01-1.10)	0.011	--	--
<i>Albumin (g/L)</i>		0.96 (0.91-1.000)	0.052	--	--
<i>Haemoglobin (g/L)</i>		1.01 (0.99-1.03)	0.322	--	--
<i>Sodium (mmol/L)</i>		0.97 (0.90-1.04)	0.382	--	--
<i>Sodium (mmol/L)</i>					
< 135	10 (4-25)	Ref.		--	--
≥ 135	16 (6-48)	0.62 (0.36-1.09)	0.097	--	--
<i>Potassium (mmol/L)</i>		0.96 (0.60-1.56)	0.876	--	--
<i>Magnesium (mmol/L)</i>		1.32 (0.1-15.74)	0.826	--	--
<i>Phosphate (mmol/L)</i>		0.41 (0.12-1.39)	0.153	--	--
<i>Adjusted calcium (mmol/L)</i>		1.48 (0.29-7.61)	0.642	--	--
PN requirements					
<i>Volume (L/day)</i>		1.63 (1.16-2.29)	0.005	--	--
<i>Volume (L/day)</i>					
< 2	34 (5-73)	Ref.		Ref.	
≥ 2	12 (6-27)	1.86 (1.07-3.26)	0.029	1.66 (0.93-2.98)	0.087
<i>Nitrogen (g/day)</i>		1.04 (0.96-1.12)	0.386	--	--
<i>Glucose (kcal/day)</i>		1.001 (1.000-1.001)	0.155	--	--
<i>Lipid (kcal/day)</i>		1.00 (0.99-1.001)	0.664	--	--
<i>Sodium (mmol/day)</i>		1.002 (0.998-1.005)	0.332	--	--
<i>Potassium (mmol/day)</i>		1.009 (1.001-1.016)	0.025	--	--
<i>Potassium (mmol/day)</i>					
< 60	24 (9-55)	Ref.		Ref.	
≥ 60	10 (4-20)	1.81 (1.19-2.75)	0.006	1.41 (0.90-2.22)	0.138
<i>Calcium (mmol/day)</i>		0.99 (0.90-1.08)	0.775	--	--
<i>Magnesium (mmol/day)</i>		1.03 (0.99-1.07)	0.103	--	--
<i>Phosphate (mmol/day)</i>		1.02 (1.00-1.04)	0.106	--	--
<i>Type of PN lipid</i>					
Other	12	Ref.		--	--
SMOFLipid	10	1.16 (0.73-1.85)	0.521	--	--

Figure 1. Kaplan-Meier curves for type of malignancy, HPN indication, KPS score, GPS, PN volume, and PN potassium content.



Karnofsky Performance Status and Glasgow Prognostic Score

KPS was negatively correlated with GPS, CRP and WCC, and positively correlated with albumin and weight at 0 to 3 months. GPS was strongly positively correlated with CRP and WCC, while strongly negatively correlated with albumin (Supplementary Table 1). KPS score and GPS distributions by HPN indication and type of malignancy and metastatic disease are shown in Supplementary Table 2. No significant association was noted among these variables.

HPN requirements

HPN requirements were examined according to type of malignancy, HPN indication, KPS score and GPS (Table 3). Our findings suggest a significant difference in PN volume according to HPN indication ($p = 0.005$). Patients with bowel obstruction or high output ostomy required higher volume than other indications (2328 mL, 2376 mL, 1725 mL, respectively). There was a correlating trend between lower KPS scores with higher HPN volume requirements (2426 mL vs 2165 mL, $p = 0.066$). Patients with bowel obstruction needed a higher content in nitrogen (11 g, $p = 0.003$), whilst patients with KPS score over 50 required higher PN lipid contents (607 kcal, $p = 0.021$). High output ostomies led to higher HPN sodium requirements, though this association did not reach significance ($p = 0.096$). PN potassium content was significantly higher in patients with bowel obstruction ($p < 0.0001$). There was a trend towards higher HPN content of calcium in patients with gynaecological malignancy or with bowel obstruction ($p = 0.072$ and $p = 0.051$, respectively).

Table 3. PN requirements according to type of malignancy, HPN indication, GPS and KPS score.

	volume (mL/day)	nitrogen (g/day)	glucose (kcal/day)	lipid (kcal/day)	sodium (mmol/day)	potassium (mmol/day)	calcium (mmol/day)	magnesium (mmol/day)	phosphate (mmol/day)
Total	2251 ± 626	11 ± 3	911 ± 304	573 ± 263	112 ± 61	58 ± 26	5 ± 2	10 ± 5	21 ± 10
Type of malignancy									
Gynaecological	2266 ± 611	11 ± 2	878 ± 267	610 ± 267	112 ± 57	56 ± 22	5 ± 2	10 ± 6	21 ± 10
Gastrointestinal	2231 ± 623	11 ± 3	968 ± 313	576 ± 262	112 ± 51	59 ± 25	4 ± 2	10 ± 5	22 ± 9
Other	2290 ± 711	9 ± 3	782 ± 320	477 ± 247	114 ± 100	63 ± 40	4 ± 2	10 ± 6	17 ± 9
<i>p-value</i> *	0.937	0.022	0.078	0.259	0.991	0.687	0.072	0.792	0.243
HPN indication									
Bowel obstruction	2328 ± 586	11 ± 2	938 ± 255	588 ± 256	113 ± 54	64 ± 24	5 ± 2	10 ± 5	21 ± 9
High output ostomy	2376 ± 679	9 ± 4	765 ± 434	551 ± 349	136 ± 98	36 ± 22	3 ± 2	10 ± 8	16 ± 11
Other	1725 ± 556	10 ± 2	890 ± 380	537 ± 206	85 ± 46	45 ± 24	4 ± 2	9 ± 5	21 ± 9
<i>p-value</i> *	0.005	0.003	0.129	0.764	0.096	<0.0001	0.051	0.721	0.147
KPS Score									
< 50	2426 ± 638	11 ± 3	872 ± 352	475 ± 304	105 ± 41	63 ± 27	5 ± 2	10 ± 5	20 ± 10
≥ 50	2165 ± 625	11 ± 2	948 ± 271	607 ± 230	112 ± 57	57 ± 26	4 ± 2	10 ± 5	22 ± 9
<i>p-value</i> *	0.066	0.964	0.251	0.021	0.548	0.272	0.912	0.466	0.253
GPS									
0	1952 ± 665	9 ± 3	626 ± 343	501 ± 325	97 ± 42	44 ± 23	5 ± 3	6 ± 5	17 ± 10
1	2206 ± 597	11 ± 2	964 ± 251	565 ± 220	124 ± 64	51 ± 14	5 ± 2	10 ± 6	19 ± 9
2	2203 ± 625	11 ± 3	909 ± 281	552 ± 272	95 ± 32	62 ± 28	5 ± 2	9 ± 4	22 ± 9
N/A	2392 ± 617	11 ± 3	960 ± 307	615 ± 259	126 ± 79	62 ± 29	4 ± 2	12 ± 6	23 ± 11
<i>p-value</i> *	0.201	0.058	0.013	0.570	0.105	0.122	0.156	0.020	0.278

* *p*-values are from ANOVA for type of malignancy, HPN indication and GPS and from *t*-test for KPS score. Values are presented as mean ± SD.

Discussion

We analysed the largest cohort of UK patients with advanced cancer on HPN, and examined whether survival might be predicted by demographic characteristics, medical factors, anthropometrics and nutritional status, serum blood tests, daily PN requirements, performance status and prognostic scores. Most patients required daily HPN (93.4%). Higher daily volume and potassium requirements were associated with a worse prognosis while demographic and anthropometric characteristics did not predict survival. Interestingly, upper gastrointestinal malignancies were associated with borderline significance for higher mortality. Only CRP and WCC appeared to be significant predictors of survival whereas serum albumin and sodium showed borderline significance. These findings offer potential prognostic parameters to assist multidisciplinary teams in decision making and appropriate care planning. Predictable requirements might facilitate the use of off-the-shelf PN bags enabling faster discharge from hospital and ultimately the provision of a sustainable service despite the growing number of referrals.

Multivariate analysis identified only baseline KPS score and GPS as significant predictors of survival (2, 3, 6, 11, 19, 34-39). In a meta-analysis, Naghibi, Smith and Elia (6) reported that patients with a higher performance status (defined as KPS greater than 50) survived longer than those with a KPS score less than 50 (median survival 183 days vs 91 days, respectively) (40). Bozzetti *et al.* (3, 25) described that GPS significantly correlated with three- and sixth-month survival ($p = 0.001$) and included a nomogram for predicting survival in HPN patients with advanced cancer (25, 41-44). Our results suggest that appropriate timely referral of advanced cancer patients for HPN should be promoted and encouraged among healthcare professionals as there seems to be a window of opportunity before a decline in performance status might nullify the beneficial effect of HPN and inappropriate therapies in vulnerable patients (31, 45).

The overall median length of survival in our cohort of patients receiving HPN was 14 weeks, consistent with the ESPEN guidelines of expected survival longer than 8-12 weeks, confirming appropriate indication for HPN (1, 27). Median duration of HPN in our study was 12.9 weeks consistent with reports from systematic reviews of 15 weeks (26). Finally, our study supports the hypothesis that a systemic inflammatory status, as assessed with higher GPS, CRP, and WCC is associated with a worse performance status (i.e. lower KPS score) and prognosis (9, 32).

Although cancer cachexia was prevalent in our cohort of patients, anthropometric characteristics failed to predict survival. According to the grading system by Martin *et al.* (10), the majority of our patients belonged to grade 4 (which predicts median survival 4.9 months). Intervention at this point is unlikely to improve cancer cachexia but rather offer the patient comfort during end of life at home rather than in hospital. This is a paramount aspect for the patients and their families and should be taken into consideration in decision making with realistic goals of the benefit of HPN in a sustainable and ethically correct process. It also has positive financial consequences in terms of healthcare system costs in palliative and end of life care. In our cohort, most patients supported with HPN, passed away in their homes or hospice (77.9%) rather than in hospital.

This study has several limitations. Firstly, there is the possibility of collection and selection bias due to missing data. Nevertheless, this would be minimal in our study due to a sufficiently large sample size (over 100 subjects). Secondly, as a tertiary referral centre and intestinal failure unit, UCLH's practices might be significantly different compared to other hospitals without seamless access to HPN services. Finally, discharge date was used as time point for measuring variables while other research groups have used date when PN was commenced in hospital (usually 2-4 weeks earlier than discharge) (6).

In conclusion, the present study supports the use of HPN in patients with advanced cancer and offers practical tools to assist clinical teams in decision making. It shows that patients supported with HPN are likely to die at home or hospice rather than in hospital. What is apparent is the need for timely referral, since patients with

earlier stage disease will likely have better GPS and KPS score which are associated with improved overall survival. Further education of healthcare professionals is necessary to ensure timely access to HPN for all patients with incurable cancer with an appropriate indication. Further research is needed regarding prognostic factors and quality of life in advanced cancer patients on HPN as well as the perception and experience of these patients and their families. It is imperative that HPN is used appropriately as part of an integrated sustainable palliative care plan.

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Mailing address for reprints

Dr Farooq Rahman

GI Services, University College London Hospitals

250 Euston Road, London NW1 2PG, United Kingdom

Tel. +44 (0) 20 3456 7890 Ext 79311; Fax: +44 (0) 20 3447 9217

e-mail: farooq.rahman@uclh.nhs.uk

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Supplementary Materials

Supplementary Tables

Supplementary Table 1. Spearman correlations between variables. Only correlations with $p < 0.05$ are shown. Censored cases were not included in this analysis.

Variable 1	Variable 2	Spearman's rho	p	N
Survival	CRP (mg/L)	-0.484	<0.001	55
Survival	WCC ($\times 10^9/L$)	-0.300	0.027	54
Survival	Albumin (g/L)	0.338	0.012	55
Survival	PN Potassium (mmol/day)	-0.247	0.016	94
Survival	KPS Score	0.374	<0.001	88
Survival	GPS	-0.444	0.001	55
KPS Score	Age	-0.276	0.010	87
KPS Score	Weight in clinic, months 0-3	0.401	0.031	29
KPS Score	CRP (mg/L)	-0.329	0.017	52
KPS Score	WCC ($\times 10^9/L$)	-0.523	<0.001	51
KPS Score	Albumin (g/L)	0.288	0.038	52
KPS Score	Haemoglobin (g/L)	-0.294	0.038	50
KPS Score	PN Phosphate (mmol/day)	0.230	0.032	87
KPS Score	GPS	-0.281	0.043	52
GPS	CRP (mg/L)	0.703	<0.001	55
GPS	WCC ($\times 10^9/L$)	0.529	<0.001	54
GPS	Albumin (g/L)	-0.683	<0.001	55

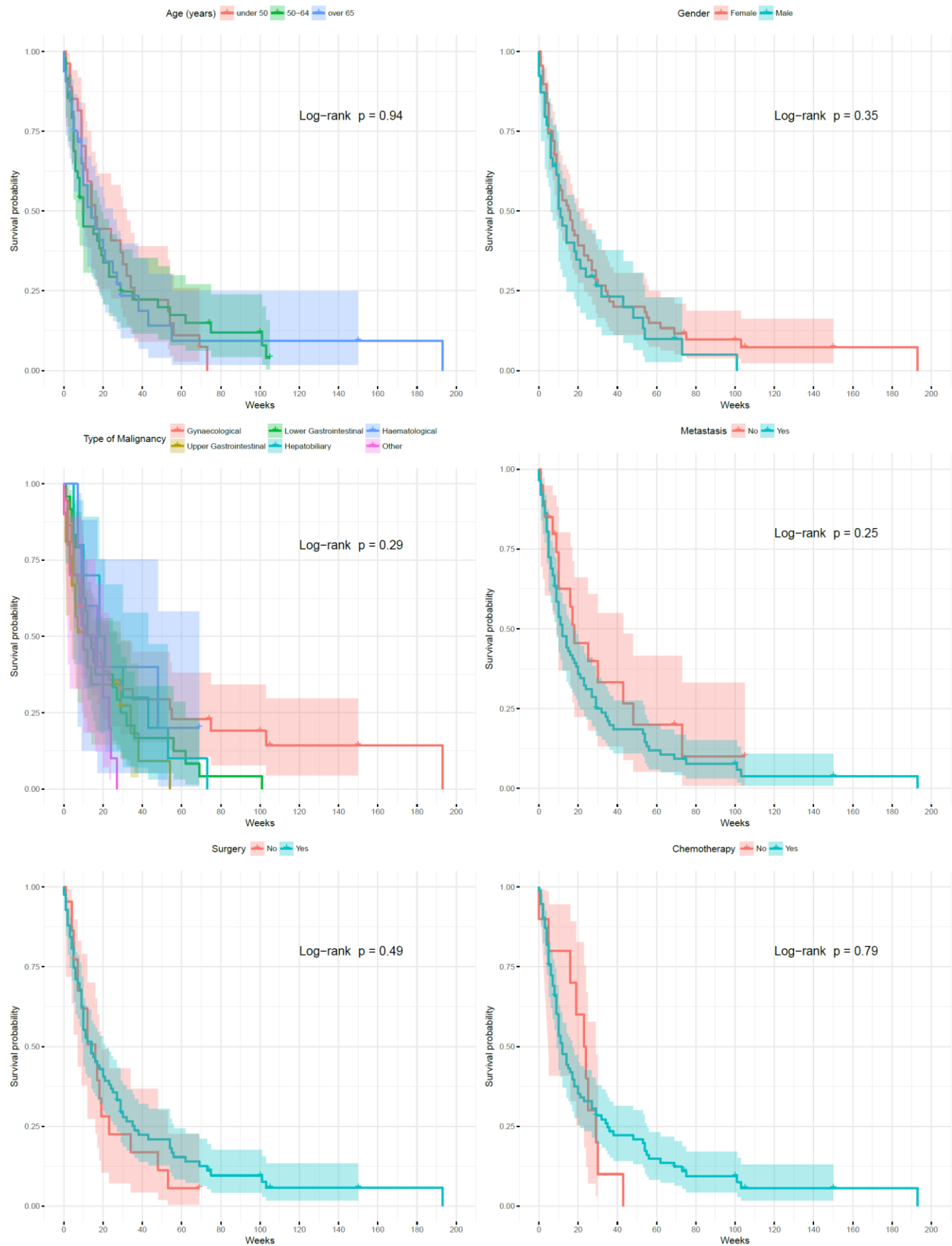
Supplementary Table 2. KPS score and GPS distribution according to type of malignancy, metastasis, and HPN indication.

	KPS Score			GPS				
	< 50	≥ 50	p^*	0	1	2	N/A	p^*
Type of malignancy								
Gynaecological	9 (25.7%)	26 (74.3%)	0.931	4 (10.8%)	7 (18.9%)	11 (29.7%)	15 (40.5%)	0.968
Gastrointestinal	15 (29.4%)	36 (70.6%)		4 (7.3%)	10 (18.2%)	20 (36.4%)	21 (38.2%)	
Other	4 (28.6%)	10 (71.4%)		2 (13.3%)	2 (13.3%)	6 (40.0%)	5 (33.3%)	
Metastasis								
No	4 (21.1%)	15 (78.9%)	0.454	3 (15.0%)	2 (10.0%)	8 (40.0%)	7 (35.0%)	0.582
Yes	24 (21.1%)	57 (70.4%)		7 (8.0%)	17 (19.5%)	29 (33.3%)	34 (39.1%)	
Indication for HPN								
Bowel Obstruction	21 (29.2%)	51 (70.8%)	0.820	5 (6.4%)	13 (16.7%)	27 (34.6%)	33 (42.3%)	0.430
High output ostomy	3 (21.4%)	11 (78.6%)		2 (13.3%)	4 (26.7%)	5 (33.3%)	4 (26.7%)	
Other	3 (25.0%)	9 (75.0%)		3 (25.0%)	2 (16.7%)	3 (25.0%)	4 (33.3%)	

* p -values are from chi-square test.

Supplementary Figures

Supplementary Figure 1. Kaplan-Meier Curve for age, gender, type of malignancy, metastasis, surgery, and chemotherapy.



Supplementary Figure 2. Kaplan-Meier Curve for radiotherapy, weight loss, BMI, cancer cachexia, parenteral nutrition lipid, and serum sodium.

